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Faculty of Pharmacy

Department of Pharmaceutical Technology

Summary of PhD. Thesis

DEVELOPMENT AND CHARACTERIZATION OF MATRIX PELLETS PREPARED BY EXTRUSION/SHERONIZATION OF ATENOLOL

Elnazeer Ibrahim Mohamed Hamedelniel

Supervisors

Prof. Dr. Klára Pintye-Hódi and Dr. János Bajdik

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Educational Program: Pharmaceutical Technology

Head: Prof. Dr. Piroska Szabó-Révész

Department of Pharmaceutical Technology

Supervisors: **Prof. Dr. Klára Pintye-Hódi and Dr. János Bajdik**

Elnazeer Ibrahim Mohamed Hamedelniel

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1. INTRODUCTION

Multiparticulate drug delivery systems are mainly oral dosage forms consisting of a multiplicity of small discrete units, each exhibiting some desired characteristics.Thus, multiparticulate dosage forms are pharmaceutical formulations in which the active pharmaceutical ingredient (API) is present as a number of small independent subunits. To deliver the recommended total dose, these subunits are filled into a sachet and encapsulated or compressed into a tablet.

Pellets for pharmaceutical applications are defined as spherical, free-flowing granules with a narrow size distribution, typically varying in diameter between 500 and 1500 μm. Pellets are a popular multiparticulate pharmaceutical dosage form that are utilized for both immediate release and a number of different controlled or special release applications. In recent years, great efforts have been made to develop controlled drug release systems via which to achieve the optimum therapeutic effect of drugs; the drug concentration is maintained in the therapeutic window for a period of time, thereby ensuring sustained therapeutic action.

Pellets can be produced in different ways: spraying a solution or a suspension of a binder and and API onto an inert core, a layering technique, spraying a melt of fats and waxes from the top into a cold tower (spray-congealing), forming pellets due to the hardening of the molten droplets, or spray-drying a solution or a suspension of the API forming pellets due to the evaporation of the fluid phase spraying a binder solution into the whirling powder using a fluidized bed. The popular method of producing pellets is by the extrusion⁄spheronization technique.

Various pharmaceutical excipients can be used to modify the release of an API from pellets formulated by extrusion and spheronization. These components form a matrix system, which ensures appropriate liberation. Different types of polymers can be

used to form soluble or insoluble systems. Their properties and the interactions between the components influence the dissolution of the API**.**

2. AIMS

Many aims are meant to ensure the preparation of matrix pellets containing Atenolol to improve its bioavailability:

The primary aim of this study was the formulation of matrix pellets containing Atenolol (Atn) by means of extrusion/spheronization with a view to increasing its bioavailability. Ethanol and water were used in various combinations as wetting liquid and their effects on the properties of the pellets formed (breaking hardness and dissolution). Was investigated. Matrix former polymer was ethylcellulose (EC).

I set out to investigate the effects of the parameters of spheronization on the properties of pellets containing Atn, microcrystallinecellulose (MCC) and EC without alkalizing components, and to determine the main factors which can influence the preparation of pellets.

Also to investigate the influence of the alkalizing components as pore-former and the wetting liquid on the formulation of pellets, and on their dissolution.

The fundamental aim of the present work was to study the delayed effects of matrix pellets coated with a gastric-resistant polymer on the release of Atn from pellets containing an alkalizing pore-former agent to ensure an appropriately alkaline micromilieu, and to improve the absorption of Atn from the intestine and therefore its bioavailability.

3. STEPS OF WORKS

In this study, the sequence that is usually applied in pharmaceutical research was followed and the work is divided into 5steps: selection of optimum matrix former from different Ethylcellulose gradients, optimum wetting liquid and operational parameters were determined, incorporation of alkalizing component as pore-former and to increase the pH at the site of Atenolol absorption in the intestine, preparation of pellets with

optimum parameters and its coating and finally *in vivo* evaluation of bioavailability of Atenolol in rats.

Applied materials

The model active pharmaceutical ingredient (API) was Atenolol (At) (Ariane Organochem Private Ltd, Mumbai,India). Ethylcellulose (EC) (Ethocel standard 4, 10 and 45 premium, Colorcon Ltd. Dartford, England) as pharmaceutical matrix former. Microcrystalline cellulose (MCC) (Vivapur 103, Rettenmaier & Söhne GmbH, Rosenberg, Germany) as pharmaceutical excipients structure former was. Ethanol 96% (Spectrum-3D, Debrecen, Hungary) and water were applied as wetting components.Trisodium phosphate dodecahydrate ($Na_3PO_4*12H_2O$) (VWR International, Belgium) and disodium phosphate anhydrous (Na_2HPO_4) (Spektrum 3D KFT Debrecen, Hungary) were used as alkalizing and pore-former agents. Opadry clear (hydroxyl propyl methylcellulose (HPMC)) and Acryl EZE MP (Colorcon Ltd., Dartford, England) were utilized as coating dispersions. The latter contains methacrylic acid copolymer (Eudragit L100-55)® as enteric coated material and plasticizer, which are necessary during coating. Dimethicone (Silfar E 1049, Wacker Chemie AG, supplier: Brenntag Hungaria Kereskedelmi Kft, Hungary) was used as anti-foaming agent.Ariavit sunset yellow CI 15985 (Sensient Food Colors Hungary Kft, Hungary), Erythrosin 6560199 (Sicopharm BASF Germany) and Indigo carmine E132 were used as dye.

1. Determination of appropriate type of Ethylcellulose and granulation liquid

Preformulation studies: water uptake

The uptake of liquids applied during pelletization is a very important parameter for the preparation of beads. The different components were tested. Table 1.

Table 1. Liquid uptakes of different samples, as Enslin numbers (ml/g)

Liquid	Type of powder				
	EC4	EC10	EC45	MCC	Atn
Water	0.05±0.01	0.07±0.02	0.15±0.01	2.76±0.04	0.07±0.02
Ethanol	0.25±0.02	0.29±0.02	0.61±0.01	1.88±0.14	1.09±0.05
Water+ethanol*	0.11±0.01	0.23±0.01	0.41±0.01	2.71±0.02	0.64±0.14

*80 ml water + 15 ml ethanol

Preparation of pellets

150 g of powder mixture was prepared from 90 g of At, 30 g of MCC and 30 g of one or other of different ECs To obtain a uniform mixture, the powder was blended at 50 rpm for 10 min with a Turbula mixer (W.A. Bachofen, Basel, Switzerland).

Samples were prepared in a high-shear granulator (ProCepT 4M8 granulator, ProCepT nv, Zelzate, Belgium) with 95 ml of granulating liquid i.e. either 95 ml of water alone, or a combination of water and ethanol (80 ml/15 ml, respectively): 15 ml of ethanol was added before or after the addition of 80 ml of water, or the two were added already mixed together.

Dissolution

On the basis of the liquids uptake results, pellets were prepared and tested (Table 1).The drug release from the pellets was studied with different dissolution kinetic models (first-order, Higuchi, Hopfenberg, RRSBW and Langenbucher). The results showed that the dissolution profile of the samples could be fitted best ($R^2 > 0.95$) with first-order kinetics (Eq. 1), as is expected for the dissolution of water-soluble drugs from porous matrices.

$$M_t = M_0(1 - e^{-kt}) \quad (1)$$

where M_t is the amount of API released from the preparation in time t, M_0 is the total amount of the drug, and k is the dissolution rate of the process. However, even this model was unable to handle the presence of a lag time, which can be observed especially in the case of samples prepared with ethanol. The dissolution was fitted with the Chapman-Richards growth model (Eq. 2), which contains a shape parameter of the sigmoid-shaped curve (Figs 1-3), and can describe the lag time:

$$M_t = M_0(1 - e^{-kt})^c \quad (2)$$

where M_t is the amount of API released from the preparation in time t, M_0 is the total amount of the drug, k is the dissolution rate of the process, and c is the shape parameter of the curve, which refers to the observed lag time of the dissolution. The dissolution rates and shape parameters are displayed in Table 3.

The results were analysed with a two-way ANOVA model. The results showed significant differences in the rates of dissolution of the samples. On the basis of these statistical differences, the samples can be divided into three groups. The highest dissolution rates were observed for samples S2B and S3C, those for samples S3B and S4C were one-tenth less, and the other samples displayed even lower dissolution rate constants (Table 2).

Table 2. Dissolution rate constants and correlation coefficients of dissolution curves

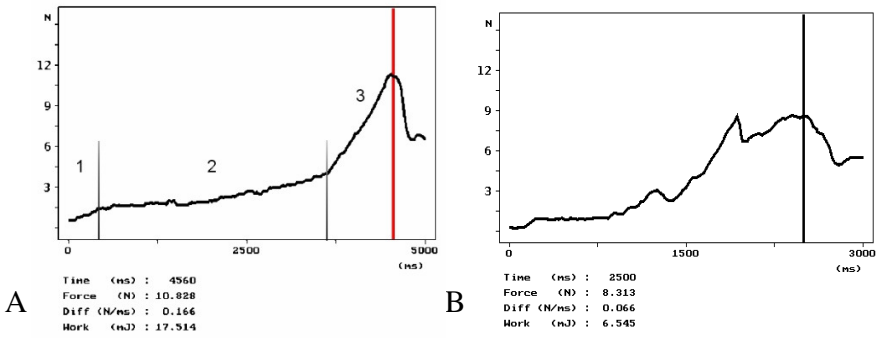
Sample		R^2 values	Dissolution rate constants	Shape parameter
S1	A	0.9968	0.04	1.35
	B	0.9919	0.03	1.40
	C	0.9956	0.05	1.70
S2	A	0.9951	0.04	1.88
	B	0.9928	0.07	3.73
	C	0.9870	0.04	1.66
S3	A	0.9871	0.04	2.32
	B	0.9875	0.05	2.66
	C	0.9929	0.07	3.74
S4	A	0.9903	0.03	2.16
	B	0.9968	0.04	3.10
	C	0.9895	0.05	2.09

Mechanical properties of pellets

The evaluation of the process of pellet deformation involved not only determination of the breaking hardness, but also study of the deformation curve. The shapes of the breaking curves of the pellets were very similar for the samples prepared with water (Fig. 1). They mainly comprised three phases: The first section (Fig. 1A:1) is indicative of elastic deformation. The pellet behaves as a Kelvin body, in which the Hooke component dominates. The relationship between the loading and the stress can be written as follows:

$$t = E(d - \delta) \qquad (3)$$

where t = the Cauchy stress tensor, E = the elasticity modulus, d = the tensor of deformation and δ = unit tensor.



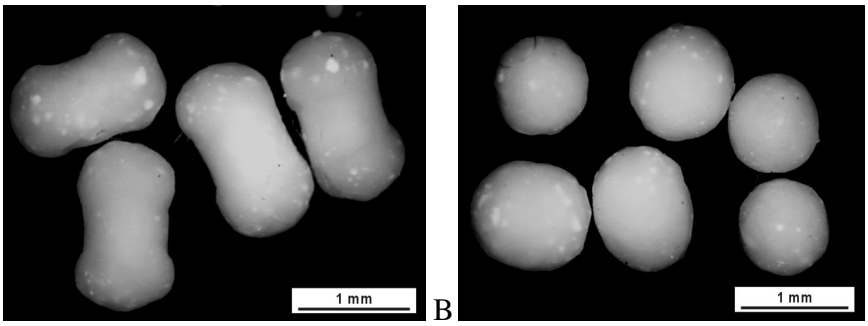
A B

Fig. 1. Deformation curves of pellets

2. Determination of the optimum wetting liquid and operational parameter of pelletization of mixture.

During the process of extrusion/spheronization, determination of the main factors which can influence the preparation of pellets is very important. A 2^3 full factorial design was utilized to optimize the circumstances applied during pelletization. The effects of the parameters of spheronization on the shape of the pellets and on the dissolution were tested. The effects of the nature of the wetting liquid applied for pelletization on the parameters of the final pellets were also examined. The spheronization was carried out according to the factorial design (2^3).

The shapes of the pellets were very different for the different samples .Better results (lower values of the aspect ratio), i.e. nearly spherical products, were observed for the particles prepared with water.Fig.2



A B

Fig. 2A and B A samples prepared.with of water/ethanol B water alone

The situation was similar for the breaking hardness of the samples (Table 3). The evaluation of the process of pellet deformation involved not only determination of the

breaking hardness, but also study of the deformation curve. The effect of the residual solvent on the mechanical properties of the spheres was neglected, because it was less than 0.5% for every sample.

The release of the active agent was sensitive to the nature of the kneading liquid. It was slower for the samples prepared with the mixture than for the samples prepared only with water

Table 3. Parameters of different pellets

Sample	Aspect ratio	Breaking hardness (N)	Dissolution at 30 min (%)	Breadth (µm)	Length (µm)	Water content (%)
S1	1.54±0.28	12.00±1.80	37.55±2.54	1491.4±142.6	2303.6±484.1	0.23
S2	1.75±0.40	13.84±2.00	31.46±5.30	1430.3±118.2	2519.1±643.3	0.27
S3	1.61±0.32	12.20±1.76	36.91±3.72	1439.6±93.0	2326.9±502.1	0.30
S4	1.38±0.19	11.70±1.89	51.06±2.43	1478.8±69.2	2035.8±281.9	0.23
S5	1.33±0.16	12.68±1.19	66.70±5.64	1450.7±64.7	1928.3±274.8	0.27
S6	1.55±0.27	15.53±1.71	67.97±2.50	1430.3±102.5	2235.3±465.1	0.40
S7	1.49±0.25	13.55±1.69	62.27±6.81	1429.3±88.7	2138.1±339.8	0.23
S8	1.17±0.09	12.45±1.38	54.13±5.66	1455.7±50.2	1705.3±155.9	0.23

Evaluation of effects of factors

A linear approach was applied for the fitting, and the correlation coefficient (R^2) was very good in every case (Table 4). The duration of spheronization was found to be a significant factor as concerns the shape of the pellets. Its negative value indicated that

increase of the duration enhanced the shape of the particles. The presence of ethanol in the wetting liquid destroyed the efficiency of the spheronization process.

The duration of spheronization was also significant for the breaking hardness of the spheres. The two other factors were similarly important. Increase of the value of each of the factors caused a decrease in this parameter. It is known that the shape can modify the breaking hardness of different systems (mainly for tablets). In the present case, there was no obvious connection between the relevance of the factors for shape and breaking. Modification of the internal structure of the spheres must therefore be responsible for this phenomenon. Formation of a mass with plasticity appropriate for spheronization was not possible with the liquid containing ethanol. Suitable wetting of MCC could not be achieved with the liquid with this composition. The squeezing of this liquid during spheronization can also be quicker, and thus the formation of an adequate structure, which is formed by MCC, was also disturbed. This process was enhanced by high speed and the duration of spheronization, which can be the explanation of the negative sign of these factors.

Table 4. Values of coefficients

Factor	Coefficient for aspect ratio	Coefficient for breaking hardness	Coefficient for dissolution
Intercept	1.4763	12.9913	50.6838
(1) Ethanol	0.0913	-0.5588	-11.4413
(2) Speed	-0.0663	-0.5188	-0.2363
(3) Duration	-0.1238*	-0.7888*	1.0313
1 by 2	-0.0113	0.0363	4.9738
1 by 3	0.0113	0.2013	4.0263
2 by 3	-0.0163	0.3863	-0.1738
R^2	0.9973	0.9983	0.9731

3. Incorporation of alkalizing component

Introduction of an alkalizing component is important to increase the pH at the site of absorption during parallel release of Atn from the matrix pellet in the micromilieu, to act as pore former, and also to lead to bridge formation during drying (crystal formation). In this work, Na_2HPO_4 or Na_3PO_4 was used as alkalizing component.

The shape and surface of the pellets depend on the consistency of the mass. This phenomenon can influence the solubility of the components. Atn dissolves sparingly in water, but is soluble in alcohol. The water solubility of anhydrous Na_2HPO_4 and Na_3PO_4 is very good, but the latter dissolves in better water. These components are insoluble in alcohol. It is well known that the solubility of EC in alcohol is very good.

For the pellet containing MCC, the binding forces can be assigned to its 'crystallite-gel model', MCC particles are broken down into smaller units and even partly into single crystals of colloidal size during granulation and extrusion in the presence of water. The resulting crystallites and porous particles form a coherent gel-like network (with a high fraction of an insoluble solid phase) and immobilize the liquid. Over a particular range of water, which relates to acceptable gel strength, extrusion and spheronization become possible.

In the samples which contained Na_3PO_4 and the wetting liquid was water alone in higher amount, the alkalizing component could take up the water from the powder mixture. This effect improves the plasticity of the wetted mass and enhances the spheronization, and is therefore a pellet structure- forming parameter which can determine not only the shape, but also the mechanical properties. During drying, rather fast recrystallization of Na_3PO_4 resulting in strong solid bridges between the other particles, e.g. MCC (P2, Fig. 3). The shape of the pellets was spherical, and the surface was smooth with some narrow or round pores, formed during drying. It could be seen at higher magnification that the texture of the pellet was very compact (Fig. 4) the hardness of these pellets was very high. On reduction of the water amount, the degree of recrystallization also decreased, but in spite of this the hardness was very good.

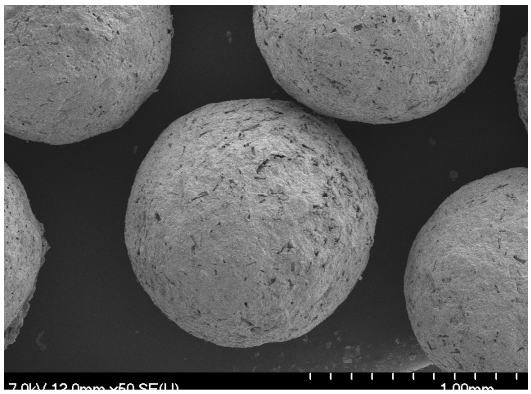


Fig. 3. Shape of P2 pellets (SEM)

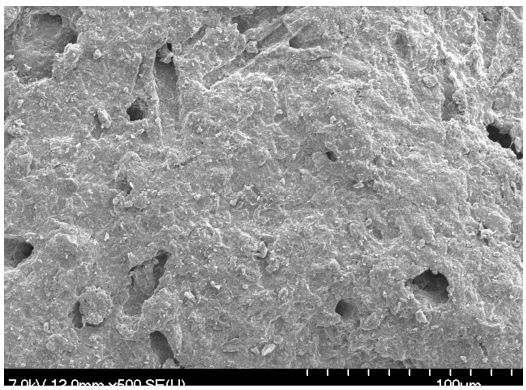


Fig. 4. Detail of surface of sample P2 (SEM)

4. Preparation of pellets with optimum parameter and its coating.

As regards the final dosage form, the pellets containing Atn should be coated with intestine-soluble polymer. In accordance with the morphological observation and the hardness of pellets, the dissolution results indicated that the P2 pellets had the best composition, suitable for the development of the final dosage form.

For the coating process, P2 pellets were prepared again and other compositions too, without and with Na_3PO_4 (Table 5)

Table 5. Preparation of pellets with different contents

Samples	Sample contents						Coating		
	Atn %	Na_3PO_4 %	MCC %	EC %	Lactose %	Water ml	Opadry %	Acryl-EZE MP %w/w	Dye
B0	25	25	30	20	-	85	3	17	
B1	25	25	30	-	20	85	-	-	-
B2	25	-	30	20	25	85	-	20	-
B3	25	-	30	-	45	85l	-	20	-

The optimum properties of the pellets (round shape, hardness and dissolution) were obtained for samples B0, B2 and B3, but not for B1, which failed in the granulation step, producing a very sticky plastic mass, resisting extrusion and hence spheronization, this being due to the interaction that occured between the alkalizing component and lactose. The reason is that lactose is incompatible with many APIs. It forms Schiff bases with primary amino groups (present in Atn) and alkaline materials promote the decomposition. Subcoating materials have been widely used to prevent interactions between an API and an enteric coating. Our formula B0 contained a high amount of a strong alkalizing agent, which influenced the dissolution of the Atn earlier than required. The alkalizing component has very good water solubility and could dissolve in the water component of the coating dispersion, so that some of it could migrate into the polymer film. Accordingly, it was necessary to protect the core before the functional coating. The protective layer used was HPMC (Opadry clear) (mass 3% w/w). After drying of the protective layer (10 min), the coating was continued with the functional, pH-dependent polymer dispersion (Acryl EZE MP). There was no need for a subcoating layer for samples B2 and B3, because there was no alkalizing component in their compositions.

5. In vivo evaluation of bioavailability of At in rat.

Dissolution tests (*in vitro)* are applied as a tool with which to predict drug product performance *in vivo*. The dissolution curves in Fig. 5 demonstrate that the Atn could not dissolve in the gastric juice, but there was a small difference in dissolution profiles in the intestinal juice (Fig. 5). The total amount of Atn dissolved from sample B3 during 150 min. Moderate dissolution took place in the case of B2. The dissolution of Atn decreased slightly in the case of B0, and the total amount of Atn dissolved during 250-300 min. These pellets were double-coated pellets.

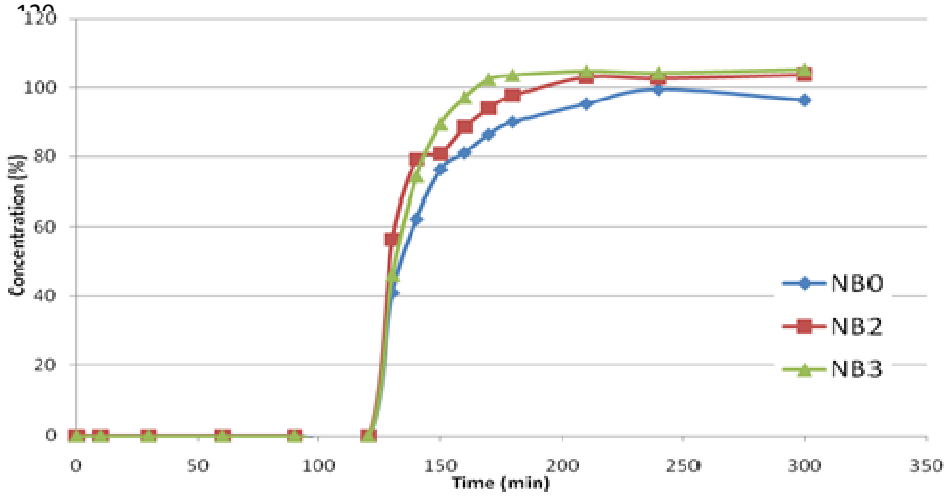


Fig 5. Dissolution profile of coated pellets in fluid of pH 1.2 for first 2 h, then continued in buffer of pH 6.8

The complete release of Atn was achieved from all samples *in vitro,* but the dissolution conditions do not fully represent the environment in the gastrointestinal tract, and the results can be interpreted only on an empirical basis. In the *in vitro* tests, the solubility of the Atn was determined. Measurement of the absorption of Atn under these circumstances is not possible.

The compositions of the media were fine-tuned according to the phase of digestion both in the stomach and in the intestines. These and other physiological and chemical factors can dramatically affect drug solubility and dissolution in the upper small intestine, and hence the rate of absorption. To study the bioavailability of Atn in rats after oral administration of 6.0 mg in capsules, the plasma was collected and analysed by HPLC. The HPLC curves revealed a high peak level in the plasma and hence the area under the curve for sample B0 was much greater than those for samples B2 and B3 (Fig. 6).

It may be concluded that the alkalizing component enhances the absorption of Atn from matrix pellets prepared by an extrusion/spheronization technique and containing EC as matrix-former.

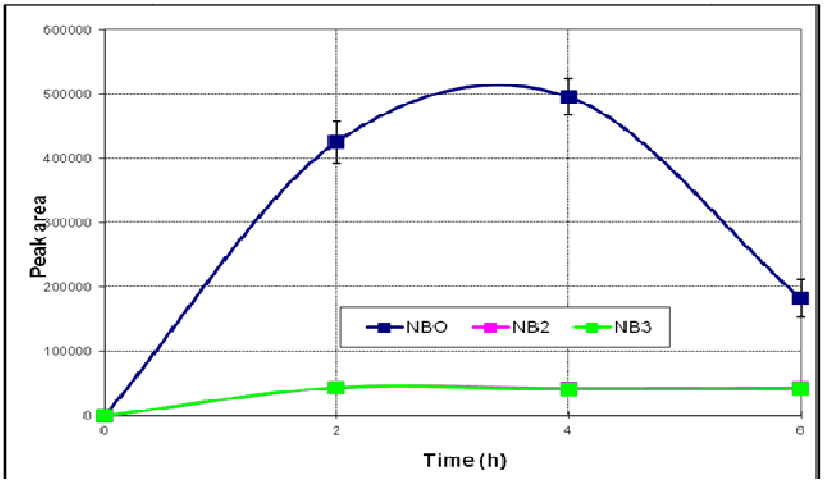


Fig. 6. HPLC plasma concentration – time curve of pellets in rats

CONCLUSION

The main aim of this work was the formulation of matrix pellets containing Atn by means of extrusion/spheronization with a view to increasing its bioavailability.

On the basis of this study, it can be concluded that water or different water/ethanol combinations are appropriate for the formulation of pellets from powder mixtures containing different ECs, MCC and Atn.

The dissolution profiles of the samples prepared with water followed first-order kinetics. For the samples where the granulating liquid also contained ethanol, the dissolution changed, and a lag time was observable. In this case, the ethanol dissolves the EC, and in the drying period an EC film was formed around the drug particles, this layer delaying dissolution. Finally, it may be stated that the application of ethanol in the wetting liquid led to a decrease in the dissolution in the first phase, but also caused a reduction in the breaking strength of the pellets. The formation and the structure of the pellets differed for the sample prepared with liquid containing ethanol.

The use of a factorial design confirmed that significant effects were exerted not only by the operational parameters, but also by the nature of the wetting liquid. Besides the shape, the internal structure of the pellets was changed by the optimum combination of factors, as indicated by the mechanical properties of the spheres and the dissolution of the active agent. The presence of ethanol in the liquid caused different degrees of wetting

in the different components of the powder mixture. This step of our work is of help in the design of pellets containing an alkalizing component for increase of the bioavailability of the active agent.

In order to enhance the bioavailability of Atn from pellets, alkalizing components (anhydrous Na_2HPO_4 and Na_3PO_4) were used. It can be concluded that the shape parameters of the pellets were best when Na_3PO_4 was the alkalizing component. As concerns the wetting liquid, the higher amount of water alone resulted in pellets with the best compact texture, with a smooth surface and considerable hardness. MCC formed a coherent gel-like network and the water-soluble Na_3PO_4 underwent rapid recrystallization, resulting in strong solid bridges with the other particles. It is clear that the alkalizing component is able to increase the pH in the micromilieu. This effect is presumably manifested in the intestine too.

In the *in vitro* experiments, the dissolution release complied with the texture of the pellets and the effect of pH. The most uniform and total release of Atn was observed for the sample containing Na_3PO_4 and prepared with water alone, which also has a very good hardness and a round shape, and which is suitable for coating and further investigation.

The results of the experiments revealed that the pellets prepared by extrusion and spheronization were spherical and had high strength. This product was suitable for coating. The *in vitro* dissolution tests demonstrated that the alkalizing component promoted the dissolution of the total amount of Atn from the pellets at pH 6.8, but use of a protective polymer layer was necessary before the functional polymer coating. This double-coated pellet is an excellent product which is suitable for filling into capsules.

Finally, the alkalizing component enhances the absorption of Atn from the matrix pellet prepared by the extrusion/spheronization technique.

FINAL CONCLUSION, NOVELY, PRACTICAL USEFULNESS

1. To achieve optimum properties of matrix pellets containing Atenolol and increasing its bioavailability:
2. Extrusion / spheronization method is very good method to prepare pellet containing ethylcellulose, microcrystalline cellulose and atenolol.
3. Ethylcellulose polymers can be used as matrix former in preparation of pellet with extrusion/ spheronization technique.
4. Microcrystalline cellulose is necessary for the formulation of good mass as it is formulation behavour.
5. Factorial design is important to evaluate factors and parameters process during pellet formulation.
6. Alkalizing components act as poreformer which improved dissolution of Atenolol and also increase the pH micromilieu parallel release with atenolol.

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